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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/788,466	03/01/2004	Steven Louis Shafer	44893-0004	9229

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SUITE 2400
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EXAMINER	
ALSTRUM ACEVEDO, JAMES HENRY	
ART UNIT	**PAPER NUMBER**
1616	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/788,466	SHAFER ET AL.	
	Examiner	Art Unit	
	James H. Alstrum-Acevedo	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17-48* is/are pending in the application.

4a) Of the above claim(s) *37-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17-36 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 17-48 are pending. Applicants have cancelled claims 1-16. Applicants have amended claims 17-22. Claim 48 is new. Claims 37-47 are withdrawn from consideration as being drawn to a non-elected invention. Receipt and consideration of Applicants' amended claim set and remarks/arguments submitted on January 12, 2007 are acknowledged. **Claims 17-36 and 48 are under consideration in the instant office action.** Applicants amended claim set have necessitated new rejections (e.g. 112, 1st paragraph [new matter]).

Moot Rejections/objections

All rejections and/or objections of claims 1-16 cited in the previous office action mailed on July 14, 2006 **are moot**, because said claims have been cancelled.

Specification

The objection to the specification for the improper use of the STELLA® trademark set forth on page 3 of the office action mailed on July 14, 2006 **is withdrawn**, per Applicants amendments to the specification capitalizing said trademarks.

Response to Arguments

Applicant's arguments, see page 13, filed January 12, 2007, with respect to the objection to the specification for the improper use of the trademarks have been fully considered and are persuasive. The objection to the specification for the improper use of the trademarks has been withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 18 has been amended to recite a total opioid concentration between 250 to 1,500 mcg/ml. The instant specification lacks written support for a total opioid concentration between 250 to 1,500 mcg/ml. Although there is explicit support for a total opioid concentration ***from*** 250 to 1,500 mcg/ml, there is insufficient written description to support a total opioid concentration ***between*** 250 to 1,500 mcg/ml. The amendment of the word "from" to "between" has resulted in a claimed range having a different scope, which does not include the stated range end points of 150 and 1,500 mcg/ml, respectively. This represents new matter, because a total opioid concentration ***between*** 250 to 1,500 mcg/ml is not supported in the specification.

Claim 48 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an opioid formulation comprising either (1) fentanyl and liposomally encapsulated fentanyl or (2) the combination of (a) remifantanil, alfentanil, sufentanil, or fentanyl and (b) methadone, wherein said formulation exhibits a pharmokinetic profile substantially similar to that depicted in Figure 18, does not

reasonably provide enablement for an opioid formulation comprising any two opioids and exhibiting a pharmokinetic profile substantially similar to that depicted in Figure 18. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. An analysis based upon the Wands factors is set forth below.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In *Genentech Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993),. See also *Amgen Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman (230 USPQ 546, 547 (Bd Pat App Int 1986)). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and (8) the breadth of the claims.

Breadth of Claims/ Nature of the invention

Applicants' claim is broad, because it claims the mixture of any two opioids in combination with any excipient. Claim 48 requires that the mixture of any two opioids exhibit a pharmacokinetic profile "substantially similar" to that depicted in Figure 18 of the instant application. The instant specification does not define or explain what is a substantially similar pharmacokinetic profile.

State of the Prior Art

The pharmacokinetic profile of liposome-encapsulated fentanyl is known in the prior art (Hung, O. R. et al. "Pharmacokinetics of Inhaled Liposome Encapsulated Fentanyl," *Anesthesiology*, **1995**, *83(2)*, 277-284). It is known in the art that one can increase the encapsulation efficiency of fentanyl merely by changing the amount of soy phospholipid used to make the liposomes (Tan, S. et al. "Sustained Tissue Drug Concentrations Following Inhalation of Liposome-Encapsulated Fentanyl in Rabbits," *Drug Delivery*, **1996**, *3(4)*, pp 252, left column). Thus, the ratio of free fentanyl to liposomally encapsulated fentanyl is an optimizable parameter. It is known in the prior art that opioids (e.g. fentanyl) can be toxic, result in serious side effects, and/or be lethal if given in inappropriate concentrations (instant specification, [0087]-[0088]; Drug Information Handbook, Lexi-Comp, Inc.: Hudson, OH, 1999-2000, pp 37-39, 414-416, 651-652, and 1099-1100). It is well known that opioid response is highly individualized (instant specification, [0087]).

Level of One of Ordinary Skill & Predictability/Unpredictability in the Art

The level of a person of ordinary skill in the art is high, with ordinary artisans having advanced medical and/or scientific degrees (e.g. M.D., Ph.D., Pharm. D. or combinations thereof). There is a general lack of predictability in the pharmaceutical art. *In re Fisher*, 427, F. 2d 833, 166, USPQ 18 (CCPA 1970).

Guidance/Working Examples

Applicants have provided guidance in the specification in the form of working examples, figures, and computer-simulated pharmacokinetic profile models based on the STELLA®

computer language. Said guidance is limited to pulmonary formulations comprising the combination of (1) a rapid onset opioid and (2) a slow onset opioid. Applicants have provided no guidance regarding the combination of two rapid onset opioids or two slow onset opioids. Furthermore, given Applicants' disclosure that their invented formulations specifically require the combination of (1) a rapid onset opioid and (2) a slow onset opioid, one must conclude that Applicants are not enabled for the combination of any two opioids in a pulmonary formulation that yields a pharmacokinetic profile "substantially similar" to that depicted in Figure 18 of the instant application. Thus, Applicants' specification is only enabling for an opioid formulation comprising either (1) fentanyl and liposomally encapsulated fentanyl or (2) the combination of (a) remifantanil, alfentanil, sufentanil, or fentanyl and (b) methadone, wherein said formulation exhibits a pharmokinetic profile substantially similar to that depicted in Figure 18.

To emphasize this point the Examiner points Applicants to "Genentech, 108 F.3d at 1366 and *Brenner v. Manson,* 383 U.S. 519, 536, 148 USPQ 689, 696 (1966)" which states,

> "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 48 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "similar" in claim 48 is a relative term, which renders the claim indefinite. The term "similar" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term similar renders the alluded to pharmacokinetic profile of the claimed formulation indefinite.

The term "substantially" renders claim 48 vague and indefinite, because an ordinary skilled artisan would be unable to ascertain what constitutes a substantially similar pharmacokinetic profile curve as shown in Figure 18. The term "substantially" is not defined in the specification. Thus, the metes and bounds of a substantially similar pharmacokinetic profile curve would be undeterminable to an ordinary skilled artisan.

Claim 48 is vague and indefinite because it requires a reader to reference an outside figure. Thus, upon solely reading claim 48, an ordinary skilled artisan would be unable to ascertain what is the required pharmacokinetic profile curve exhibited by the claimed formulation.

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The rejection of claims 18-20, and 22-28 under 35 U.S.C. 102(b) as being anticipated by Mezei et al. (U.S. Patent No. 5,451,408) **is withdrawn** per Applicants claim amendments changing the dependency of claims 18-20 and 22-28 to depend from claim 17.

Response to Arguments

Applicant's arguments, see page 13, filed January 12, 2007, with respect to the rejection of claims 18-20, and 22-28 under 35 U.S.C. 102(b) as being anticipated by Mezei et al. have been fully considered and are persuasive. The rejection of claims 18-20, and 22-28 under 35 U.S.C. 102(b) as being anticipated by Mezei et al. has been withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Applicant Claims
2. Determining the scope and contents of the prior art.
3. Ascertaining the differences between the prior art and the claims at issue, and resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out

the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 17, 21, and 29-36 under 35 U.S.C. 103(a) as being unpatentable over Mezei et al. (U.S. Patent No. 5451408) **is maintained** for the reasons of record set forth on pages 3-8 of the office action mailed on July 14, 2006 and further articulated below. Claims 18-20, 22-28, and 48 are appended to this rejection for the reasons of record. In summary, **claims 7-36 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mezei et al. (U.S. Patent No. 5451408).**

Response to Arguments

Applicant's arguments filed January 12, 2007 have been fully considered but they are not persuasive. Applicants' traversal of the instant rejection is based on the following arguments: (1) unexpected results have allegedly been demonstrated from the claimed parameters; (2) the prior art is silent on the alleged problem of "titrating to effect" and patient self-administration; and (3) the prior art is silent on the use of the claimed formulations for titration to effect self-administration.

The Examiner respectfully disagrees with Applicants' traversal arguments. Regarding argument (1), it is noted that nowhere in the specification is it stated that the data presented is a demonstration of unexpected or surprising results. Applicants' remarks/arguments submitted January 12, 2007 is the first instance on the record in which there has been any mention of alleged or unexpected results. Regarding the allegation of unexpected results, Applicants'

assertion is not persuasive, because the instant specification does not contain data comparing different ratios of free fentanyl to liposomally encapsulated fentanyl. There is no objective evidence of record that supports Applicants' assertion of alleged unexpected results and thus, Applicants' claimed ratio of free fentanyl to liposomally encapsulated fentanyl merely represents a routine optimization in the amounts of free fentanyl and liposomally encapsulated fentanyl. Regarding the combination of alfentanil and morphine and the relative amounts of these two opioids, Applicants' specification lacks any objective evidence demonstrating that the claimed combination of these specific two opioids in the claimed ratios and relative amounts demonstrates an unexpected property or result, in comparison with the other binary opioid combinations and/or different relative amounts of alfentanil and morphine.

Regarding Applicants' arguments (2) and (3), it is confusing how the same thing "titrating to effect" can simultaneously be argued as being an alleged problem and also a known use. This line of argument is inconsistent. Notwithstanding this, the prior art is not required to teach the same use as disclosed by Applicants, especially when it is noted that the claims under examination are composition claims, not methods of use. Arguments (2) and (3) are unpersuasive and the instant rejection is deemed proper. Therefore, the claimed invention, as a whole, would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, because the combined teachings of the prior art is fairly suggestive of the claimed invention.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The rejection of claims 17-18 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 10-25 of U.S. Patent No. RE38407 **is maintained** for the reasons of record set forth on page 9 of the office action mailed on July 15, 2006.

Response to Arguments

Applicant's arguments filed January 12, 2007 have been fully considered but they are not persuasive. Applicants' traversal of the instant rejection is based on the following arguments: (1) unexpected results have allegedly been demonstrated from the claimed parameters; (2) the prior art is silent on the alleged problem of "titrating to effect" and patient self-administration; and (3) the prior art is silent on the use of the claimed formulations for titration to effect self-administration.

These arguments are the same arguments discussed previously in the instant office action. The Examiner's position regarding these arguments is the same and is reapplied to the instant rejection. Thus, the instant rejection remains proper.

The provisional rejection of claims 17-21, 29-30, and 33 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-8 and 10-11 of copending Application No. 10/927,145 (copending '145) **is maintained** for the reasons of record set forth on page 9 of the office action mailed on July 15, 2006.

Response to Arguments

Applicants have requested that the instant rejection be held in abeyance until the claims of the instant application or those of copending '466 are in condition for allowance. Neither application is in condition for allowance at this time, thus the instant rejection is maintained.

Conclusion

Claims 17-36 and 48 are rejected. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James H. Alstrum-Acevedo whose telephone number is (571) 272-5548. The examiner can normally be reached on M-F, 9:00-6:30, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann Richter can be reached on (571) 272-0664. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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